ESTTA Tracking number: **ESTTA469678**

Filing date: **04/27/2012**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Proceeding	92052897
Party	Defendant Galderma Laboratories, Inc.
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Date	04/27/2012
Attachments	Declaration of Cindy Kee Part 4.pdf (12 pages)(1397231 bytes)

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A New Body Moisturizer Increases Skin Hydration and Improves Atopic Dermatitis Symptoms Among Children and Adults

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ABSTRACT

Moisturizers result in an increase of skin hydration and restoration of the skin barrier function and play a prominent role in the long-term management of atopic dermatitis (AD). Cetaphil Restoraderm™ Moisturizer (CRM) contains novel ingredients specifically designed for AD, and its effects on skin hydration, skin barrier function and signs of AD were assessed in four studies, three of which were evaluator-blinded, randomized and intra-individual comparison trials. A single application of CRM induced significantly greater hydration than the untreated control for at least 24 hours ($P<0.001$). After the skin was disrupted with 0.5% sodium dodecyl sulfate (SDS), applications of CRM led to a more rapid restoration of skin barrier function and maintained significantly greater skin hydration compared to the untreated control (both $P<0.05$). After four weeks of twice-daily CRM application among subjects with a history of AD, a significant decrease of itching/stinging scores compared to baseline was reported, as well as an improvement in the quality-of-life and a high level of satisfaction regarding the product. When CRM was used as an adjunctive treatment with topical steroid for four weeks among subjects with mild–to–moderate AD, a more rapid decrease of overall disease severity was observed on days 7, 14 and 21 by the blinded investigator ($P<0.05$), compared to steroid treatment alone. In summary, CRM is suitable for the specific needs of patients with AD and can be used either alone for long-term management or in adjunction with traditional treatment for both short and long-term disease control.

J Drugs Dermatol. 2011;10(7):744-749.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory disease, with a prevalence of 2–5 percent in the general population and approximately 15 percent in children and young adults.[1] The disease is characterized by skin barrier dysfunction, which leads to increased transepidermal water loss, xerosis and secondary infection. Pruritus is a key feature of AD, which results in a vicious cycle of itching and scratching and further compromises the already damaged skin barrier. Emerging evidence from basic research provides a better understanding of the epidermal pathogenic mechanisms that may explain the barrier dysfunction found in AD, including impaired ceramide synthesis and loss-of-function mutations in the filaggrin gene.[2-4] These insights into the disease pathogenesis may provide new leads in the design of treatments better targeted to AD patients.

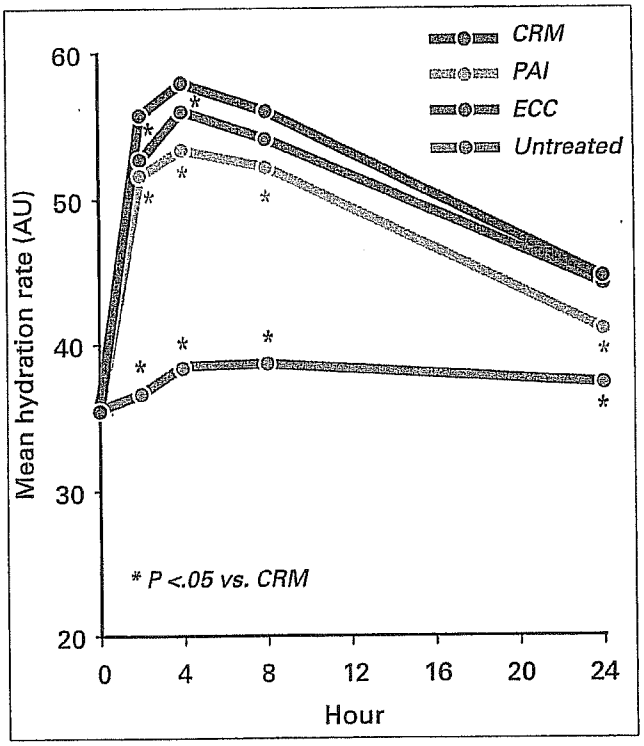
Effective management of AD presents a challenge to pediatricians and dermatologists due to the chronic and relapsing nature of the disease. Since there is no cure for AD, the treatment strategy usually involves the treatment of flares followed by long-term management using flare prevention strategies.[5] While topical steroids remain the mainstay of treatment during flares, the foundation of long-term AD management is proper skin care with the use of daily skin moisturization according to several regional and international consensus guidelines.[1,6,7] Despite the primary importance of daily skin moisturization, few data exist regarding the optimum skin care regimen in AD.

Cetaphil® (Galderma SA) is a family of non-irritating skin care products specifically designed for individuals with sensitive or compromised skin. The Cetaphil moisturizing cream was shown to have skin barrier restoration function among rosacea and acne patients.[8,9] The recently available Restoraderm™ products include a body wash and a body moisturizer (CRM), which were designed for children and adults with AD to repair skin barrier function (by using ceramides) and to increase skin hydration (by supplementing filaggrin breakdown products). In addition, the moisturizer is comprised of humectants, emollients and occlusives intended to enhance skin barrier integrity. The objectives of the present studies on CRM were to determine the effect of CRM application on skin hydration and signs of AD when used either alone or in conjunction with topical treatments.

METHODS

These four independent studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practices and local regulatory requirements. All subjects provided written

FIGURE 1. Study *A*. Mean hydration rate after a single application of CRM and two reference products (PAI and ECC) versus no treatment.



informed consent prior to entering the studies. Safety was monitored in each study by reporting of adverse events (AEs). For all studies, room humidity and temperature were controlled to remain within published guidelines,[10] and subjects were allowed to rest in the room 15 minutes prior to measurements. All diagnoses of AD were made using the Hanifin-Rajka criteria.[11]

Study A (kinetic of skin hydration after a single application of moisturizers): This was a single center, evaluator-blinded, randomized and intra-individual comparison study performed in Germany, at the proDERM Institute for Applied Dermatological Research in Schenefeld/Hamburg. Eligible subjects were male or female aged 18 to 60 years, with a history of AD and at least mild xerosis as determined by the investigator. For each subject, three non-lesional 4 cm x 5 cm areas on the volar forearms were randomized to receive one of the three test products: CRM, Physiogel® AI cream (PAI cream; Stiefel Laboratories) or Eucerin® Calming Cream (ECC; Beiersdorf), with one additional area remaining untreated to serve as a control. Skin hydration was measured by a technician blinded to randomization using a Corneometer® CM 825 (Courage & Khazaka) immediately before and 2, 4, 6, 8 and 24 hours after product application. The difference in hydration rate was analyzed using a paired *t*-test.

Study B (recovery of skin barrier function): This was a single German center (proDERM Institute for Applied Dermatological Research), evaluator-blinded, randomized and intra-individual comparison study. Eligible subjects were male or female aged 18 to 55 years, with a history of active or quiescent AD. A patch (18 mm in diameter) containing an aqueous solution of 0.5% sodium dodecyl sulfate (SDS) was applied for 24 hours to non-lesional skin on each of the four areas delineated on the volar forearms. After removal of the patch, test areas were randomized to remain untreated or to receive one of the three products (CRM, PAI and ECC) three times a day for five days. Hydration and transepidermal water loss (TEWL) were measured at days 2 and 5 using Corneometer CM 825 and DermaLab® USB Moisture module (Cortex Technology), respectively. The between-product difference in hydration and TEWL was analyzed using paired *t*-test.

Study C (tolerability and cosmetic acceptability): This was a single center, open-label study performed in the United States (Reliance Clinical Testing Services, Inc., in Irving, Texas). Eligible subjects were male or female aged 3 to 70 years, with a history of AD but no active lesions requiring treatment. Topical steroids were disallowed. Subjects were instructed to apply CRM twice daily for four weeks. At baseline and week 4, skin hydration was measured using Skincon® 200 EX (I.B.S. Co) and subjects assessed their symptoms of itching, burning and stinging, using a scale from 0 to 3. Subjects' quality of life was assessed using the Dermatology Life Quality Index (DLQI) questionnaire, a validated questionnaire adapted to each age group, completed at baseline and at week 4. At the end of the study, subjects also completed a satisfaction questionnaire. The intra-subject differences on the tolerance criteria and DLQI scores were analyzed using Wilcoxon Signed-Rank test.

Study D (efficacy when used as an adjunct to corticosteroid treatments): This was a multicenter (from three sites of Hill Top Research in the United States: St. Petersburg, Florida; Miamiville, Ohio; and Scottsdale, Arizona), evaluator-blinded, randomized and intra-individual comparison study, with visits occurring at baseline, days 7, 14, 21 and 28. Eligible subjects were male or female aged three years or older, diagnosed with mild-to-moderate AD as rated by Investigator Global Assessment. Subjects were instructed to continue their routine course of care with topical steroids, but were instructed to apply CRM twice daily on the designated half of their body and to apply no moisturizer on the other half. At baseline and day 28, skin hydration was measured using Corneometer CM 825 on the volar forearms of a subset of subjects, for both lesional and non-lesional skin. At the end of the study, subjects completed a satisfaction questionnaire. A modified Eczema Area and Severity Index (EASI) (adapted to a split body design where the constant weighted values were reduced by 50%) was assessed by the blinded investigator at each study visit. The EASI score

TABLE 1.

Study C. Mean DLQI Scores by Age Groups

	Ages 3-4 (N=4)	Ages 5-16 (N=24)	Ages >17 (N=32)
Baseline	4.00	1.13	1.34
Week 4	1.50	0.33	0.31
p-value	N.A	0.007	<.001

provides a reliable and sensitive tool to assess the severity of AD and has demonstrated good intra- and inter-observer reliability.[12,13] The within-treatment and between-treatment differences in skin hydration and EASI were analyzed using a paired t-test and ANCOVA test, respectively

RESULTS

Study A (kinetics of skin hydration after a single application of moisturizers)

A total of 30 subjects with a history of AD and dry skin were included in this evaluator-blinded, randomized and intra-individual comparison study. A majority of the enrolled subjects were female (83.3%), with a mean age of 39.5 years. All subjects completed the study and no adverse event was observed. A single application of CRM led to an immediate and significant increase of skin hydration, compared to the untreated control ($P<0.001$; Figure 1). This effect was observed from the first time point (two hours after application) and was sustained for 24 hours. When compared to the two reference moisturizers PAI and ECC, skin hydration with CRM was significantly superior to PAI at all time points and to ECC at two and four hours after application (all $P<0.05$).

Study B (recovery of skin barrier function)

A total of 30 subjects with a history of AD were enrolled into this evaluator-blinded, randomized and intra-individual study. A majority of the subjects were female (93.3%), with a mean age of 43.9 years. All subjects completed the study, except one who discontinued due to a mild adverse event possibly related to the study treatment (mild local skin irritation).

As expected, the 24-hour application of a patch with 0.5% SDS induced marked disruption of skin barrier function, as indicated by an increase of TEWL from 6.6 to an average of 28.2 g/(m²h). Repeated applications of CRM were significantly more efficacious in restoring the skin barrier function, compared to the untreated control which underwent spontaneous recovery ($P<0.05$; Figure 2A). While the inter-product differences were not statistically significant, CRM demonstrated a superior numerical trend compared to the two reference moisturizers (PAI and ECC) at both day 2 and day 5 in the reduction of

FIGURE 2. *Study B.* (A) Mean reduction over time in Trans Epidermal Water Loss (TEWL) and (B) evolution of hydration rate after SDS-induced disruption following three time daily applications of CRM and two reference products (PAI and ECC) versus no treatment.
Note: a reduction in TEWL represents an improvement in barrier function.

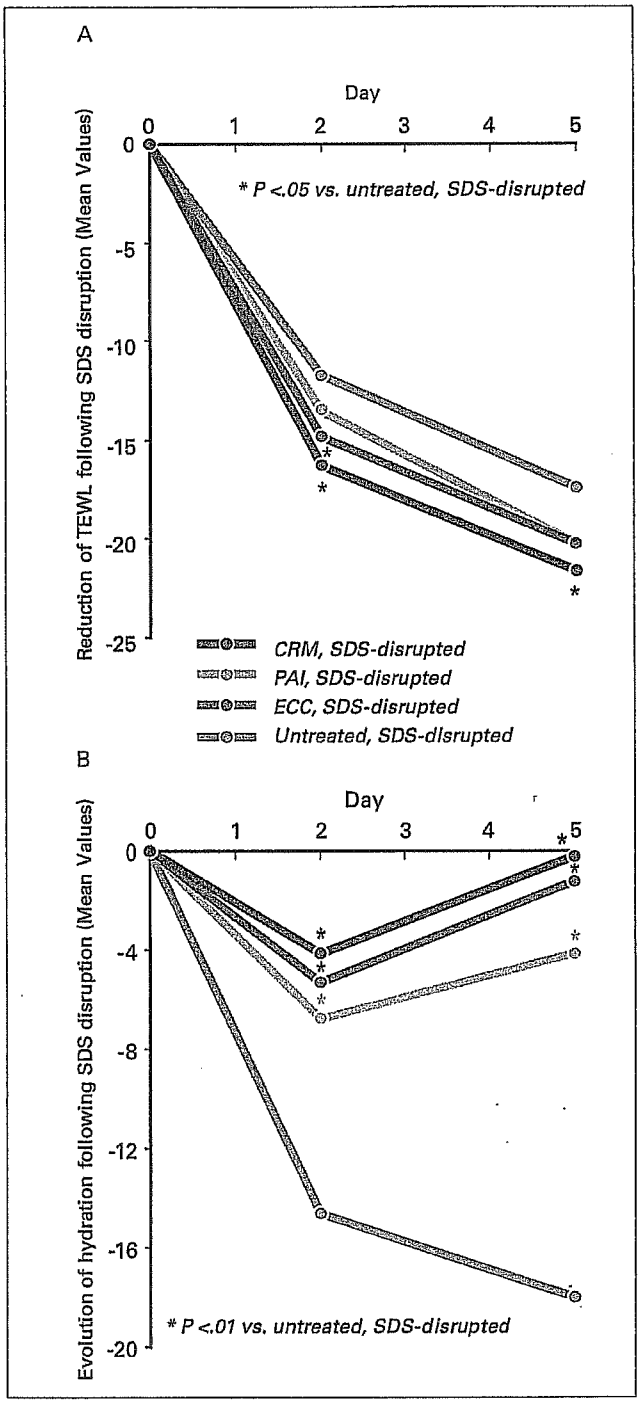


FIGURE 3. *Study D.* Mean hydration rate after one-month application of CRM.

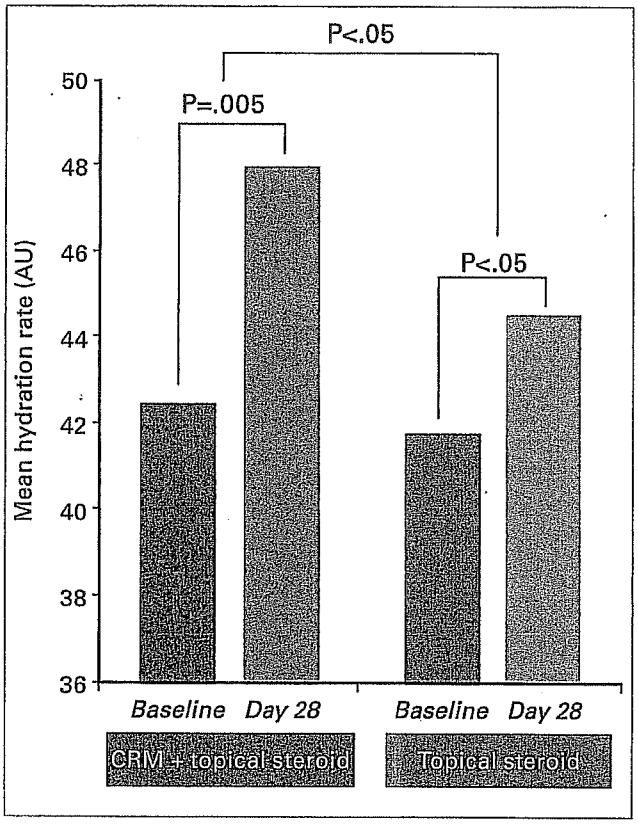
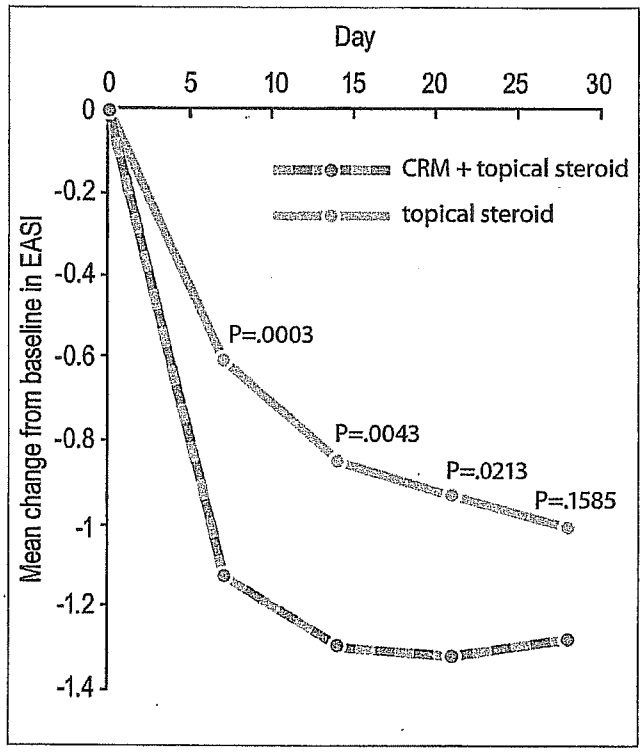


FIGURE 4. *Study D.* Mean change from baseline in EASI.



TEWL, and only CRM was significantly superior to the untreated area at day 5. The results on skin hydration were consistent with those on skin barrier function. Repeated applications of all three tested moisturizers prevented further loss of skin hydration observed for the untreated and SDS-disrupted control (all $P<0.01$; Figure 2B). CRM was numerically more efficacious than PAI and ECC at both day 2 and day 5, although the differences were not statistically significant.

Study C (tolerability and cosmetic acceptability)

A total of 66 subjects with a history of AD were enrolled into this open-label study. A majority (65.2%) of the subjects were female, with a mean age of 27.5 years. About half of the subjects were 16 years or younger. A total of 60 subjects completed the study, and no subject discontinued due to adverse events. The effect of repeated applications of CRM on skin hydration was confirmed in this study, with an increase of 35.9% at week 4 compared to baseline (63.3 Arbitrary Unit [AU] vs. 86.1AU ($P<.001$). After four weeks of CRM applications, subject-assessed tolerability scores for itching and stinging also decreased significantly compared to baseline. When the overall tolerance (i.e., chest, abdomen, arms, legs and back) was averaged for each subject, a significant decrease in itching ($P=0.001$) and stinging ($P=0.028$) was observed between the baseline and week 4 visit. High levels of subject satisfaction were reported in the questionnaire at the end of the study, with all subjects reporting a good overall impression of the product. A vast majority of the subjects (51–59 out of 60 subjects) had positive opinions about the texture, color, smell and consistency of CRM, and considered that it applies and penetrates the skin easily. After four weeks of CRM application, the score of subjects' quality of life also improved in all age groups (Table 1). The score was relatively low at baseline since the subjects were not experiencing AD flares; nevertheless, significant improvements were observed for the age groups of 5–16 and 17 and older. Due to a small subject number in the age group of 3–4, the statistical test could not be performed.

Study D (efficacy when used as an adjunct to corticosteroid treatments)

A total of 127 subjects with mild-to-moderate AD were enrolled into this multi-center, evaluator-blinded, randomized and intra-individual comparison study, and 42 of them were enrolled in a subset for corneometry/TEWL measurements. None of the subjects discontinued due to adverse events, and 123 subjects reported normal study completion. All subjects received pre-

scribed topical steroid treatments for all affected areas of their entire body, with 23.8 percent of subjects receiving steroids of class I to III potency. The subjects were instructed to apply CRM on one complete side of the body and to not apply any moisturizers on the other side on both lesional and non-lesional skin. After four weeks, a significant increase of skin hydration was reported for both sides of the body compared to baseline ($P<0.05$; Figure 3). Moreover, the side receiving both steroids and CRM also had significantly higher skin hydration compared to the other side receiving steroid treatment only ($P<0.05$). EASI decreased progressively during the treatment for both sides of the body (Figure 4). In addition, the side receiving topical steroids and CRM had a more rapid onset of action, with significantly lower EASI observed at days 7, 14 and 21 compared to the side receiving topical steroids only (all $P<0.05$). These effect sizes were small, however, as most subjects had mild disease and the mean starting EASI scores were low.

At the end of the study, subject perception of the product revealed that 84.3–96.7 percent of subjects considered that CRM reduces inflammation, relieves dry and itchy skin, provides long lasting hydration, leaves skin feeling protected, and maintains healthy skin. Moreover, 93.9–98.4 percent of subjects believed that CRM is appropriate for both adults and children, and fits the specific needs of their skin.

DISCUSSION

Restoring skin barrier function and providing superior hydration are two fundamental elements in the proper management of AD. Results of the present studies demonstrated that application of CRM on subjects with a history of AD led to an increase in skin hydration, a recovery of skin barrier function after barrier disruption, an improvement of subjects' quality of life and a high level of satisfaction. Furthermore, repeated application of CRM among children and adults with mild-to-moderate AD in addition to topical steroid treatment resulted in a modest but more rapid decrease of overall disease severity, compared to topical steroids only.

The effect of CRM on enhancing skin barrier function and hydration could be explained by its unique and patent-protected ingredients. Specifically, the filaggrin breakdown products including pyrrolidone carboxylic acid (PCA) and arginine, key components of the stratum corneum natural moisturizing factor (NMF), were supplemented in CRM to restore the hydration of the stratum corneum.[4] CRM also contains sphinganin derived sphingolipid, which could induce the synthesis of several sub-fractions of ceramides presented in lower level among AD patients and thus strengthen the skin barrier.[2,3] In addition to those novel ingredients, CRM contains humectants and emollients such as glycerol, sorbitol and sodium hyaluronate, which contribute to the increase of water content and help to restore fissured and xerotic skin.

Moisturizers with hydration properties such as CRM are the foundation of AD management, and CRM may provide several advantages when used regularly. First, increased skin hydration resulting from CRM application provides relief from itching. This treatment outcome and the accompanied improvement in quality of life could in turn enhance adherence, which represents an important challenge in the management of AD patients.[14,15] Secondly, our data suggest that repeated applications of CRM may improve skin barrier function better than routine emollients. Finally, it has been demonstrated that applications of emollients are effective not only in preventing flares among patients with established AD (secondary prevention),[16] but may represent a new strategy for preventing the onset of AD from birth (primary prevention).[17]

During flares, CRM could be used in adjunct with AD treatments to further improve treatment outcomes.[18] In the present study, while the 4-week topical steroid treatment led to a reduction of AD symptoms and an increase in skin hydration, application of CRM resulted in an even faster improvement and statistically significant greater level of skin hydration compared to steroid treatment alone, and could thus provide additional comfort to patients suffering from active AD lesions. Given the well-known potential side effects of topical steroids, such as skin atrophy, striae, and adrenal suppression,[18] the use of a moisturizer that can enhance disease clearance should result in reduced long-term topical steroid exposure. The adjunctive usage of CRM is thus of interest, since it led to a more rapid decrease of overall disease severity measured with EASI compared to steroids alone. This observation could translate into a clinically relevant corticoid-sparing effect, with less frequent or shorter durations of steroid treatment.[19]

In summary, application of the novel body moisturizer CRM, specifically designed for atopic dermatitis, leads to increased skin hydration and restoration of skin barrier function among children and adults with a history of AD. Compared to topical steroid treatment alone, adjunctive usage of CRM with steroids resulted in a greater skin hydration and a more rapid disease remission. This moisturizer with unique properties is therefore suitable for both the long-term management and the short-term treatment of atopic dermatitis.

ACKNOWLEDGMENTS

The authors would like to thank M. MA for editorial assistance.

DISCLOSURES

Dr. Simpson is a consultant for Galderma. Dr. Dutronc is an employee of Galderma.

The studies were supported by Galderma R&D.

REFERENCES

1. Darsow U, Wollenberg A, Simon D, et al. ETFAD:EADV eczema task force 2009 positiion paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venerol.* 2010;24:317-328.
2. Imokawa G, Abe A, Jin K et al. Decreased level of ceramides in stratum corneum of atopic dermatitis: An etiologic factor in atopic dry skin? *J Invest Dermatol.* 1991;96:523-526.
3. Yamamotot A, Serizawa S, Ito M, Sato Y. Stratum corneum lipid abnormalities in atopic dermatitis. *Arch Dermatol Res.* 1991;283: 219-223.
4. Palmer CAN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38:441-446
5. Simpson EL. Atopic dermatitis: A review of topical treatment options. *Curr Med Res Opion.* 2010;26:633-640.
6. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "administrative regulations for evidence-based clinical practice guidelines." *J Am Acad Dermatol.* 2004;50:391-404.
7. Ellis C, Luger T, Abeck D, et al. International consensus conference on atopic dermatitis II (ICCAD II): Clinical update and current treatment strategies. *Br J Dermatol.* 2003;148(supp):3-10.
8. Laquieze S, Czernielewski J, Rueda M-J. Beneficial effect of a moisturizing cream as adjunctive treatment to oral isotretinoin or topical tretinoin in the management of acne. *J Drugs Dermatol.* 2006;5(10):985-990.
9. Laquieze S, Czernielewski J, Baltas E. Beneficial use of Cetaphil moisturizing cream as part of a daily skin care regimen for individuals with rosacea. *J Drugs Dermatol.* 2007;18:985-890.
10. Pinnagoda J, Tupker RA, Agner T, Serup J. Guidelines for transepidermal water loss (TEWL) measurement. *Contact Dermatitis.* 1990;22:164-178.
11. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh).* 1980;92(suppl):44–7.
12. Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): Assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol.* 2001;10:11-18.
13. Barbier N, Paul C, Luger T, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol.* 2004;150:96-102.
14. Krejci-Manwaring J, Tusa MG, Caroll C, et al. Stealth monitoring of adherence to topical medication: Adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol.* 2007;56:2116.
15. Brown KL, Krejci-Manwaring J, Tusa MG, et al. Poor compliance with topical corticosteroids for atopic dermatitis despite severe disease. *Dermatol Online J.* 2008;14:13.
16. Szczepanowska J, Eich A, Szepietowski JC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatr Allergy Immunol.* 2008;19:614-618.
17. Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol.* 2010;63:587-93.
18. Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol.* 2003;21:193-200.
19. Msika P, De Belilovsky C, Piccardi N, et al. New emollient with topical corticosteroid-sparing effect in treatment of childhood atopic dermatitis: SCORAD and quality of life improvement. *Pediatr Dermatol.* 2008;25(6):606-612.

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